Amendments to the Specification:

Please replace paragraph [001] with the following amended paragraph:

[001] The present invention relates to an improved and more efficient method of producing aqueous buffers and other aqueous solutions used for various unit operations such as chromatography in the processing of biopharmaceuticals or other applications by utilizing ~~continuous generation~~ in-line preparation from common stocks of concentrated constitutive acids and bases, as well as salts and other needed reagents.

Please replace paragraph [002] with the following amended paragraph:

[002] The present invention is directed to a method of producing solutions which require pH-controlled buffers either for product processing operations or as the final product. These processes or products have in common the need to control pH, which is done through the use of a buffer compound containing ionizable groups, and adjusting the pH of the solution to within approximately 1 pH unit above or below the pKa of the ionizable groups. In this pH range, the ionization equilibrium of the ionizing groups has a buffering effect, making the pH of the solution reasonably stable to small changes in pH from chemical reactions to which it may be exposed that add or remove hydrogen ions from the solution. In current industry practice, these pH buffer solutions are usually created by making an aqueous solution of a purified salt form of the buffering compound, adding any additional solution components required for the application (such as other salts, surfactants microbial inhibitors, and the like) and then adjusting the pH of the solution up or down by the controlled addition of either acid or base (often HCl or NaOH) as required. The buffering compound and additives are most often in the form of dried (often crystalline) salts, which are relatively expensive. ~~The acid~~ Conversely, the constitutive acid or base forms of the buffering compound are often supplied as a concentrated liquid, and are most often substantially less expensive than the corresponding dried salt

Please replace paragraph [003] with the following amended paragraph:

[003] Applications for pH buffered solutions include all of the unit operations used in production and downstream purification of biopharmaceuticals, including those produced by fermentation of microbes, fungus or yeast, mammalian or insect cell culture and transgenic animal and plant sources. The unit operations which use pH buffered solutions include filtration, centrifugation, precipitation, crystallization and column chromatography. Chromatography operations in particular utilize different pH ~~buffered solutions for loading the column, washing, eluting the product, regenerating, and re-equilibrating the column~~buffered solutions for equilibrating and loading a chromatography column, washing the column and, eluting the product from it, as well as regenerating and restoring the column. Every unit operation is achieved in discrete sub-batches or cycles, with a product batch comprised of one or more unit operation cycles. Other applications for the invention might include products which themselves are pH buffered solutions. Examples of such products include ophthalmic solutions and infusion solutions.

Please replace paragraph [004] with the following amended paragraph:

[004] In these applications for this invention, the final use of the buffered solutions often requires that the solutions be aseptic, and in some cases sterile. The final blended buffer solution is often quite supportive of microbial growth. Practical production, handling and storage of aseptic or sterile solutions requires very careful, specialized and expensive design and construction of all the equipment which contacts the solution. In addition, the equipment must be subjected to rigorous clean-in-place (CIP) procedures following usage to ~~insure no chance of~~ thoroughly clean solution contact surfaces and minimize the possibility of microbial contamination being present for the next batch, and may also require steam-in-place (SIP) procedures to ~~insure sufficiently clean conditions~~insure sterile processing conditions. The water used for these applications is produced to very high purity requirements (most often water-for-injection or WFI), and is costly to utilize. These requirements for aseptic or sterile system make both the capital and operating costs of such processes very high.

Please replace paragraph [006] with the following amended paragraph:

[006] In many modernized plants tasked to the production of biopharmaceuticals, the systems designed for manufacturing unit operations require both large capital outlays and a large labor force. The state of the art is such that the current processes provide to the combination of multiple buffers, eluents, regenerants, and other solutions employed in the unit operations individually. The components for each of these numerous and various solutions are respectively mixed with the appropriate pharmaceutical grade water (such as water for injection or "WFI") in large, shared solution ~~blending~~preparation tanks. Thereafter, the resulting solution is microfiltered, tested, and transferred to individual, dedicated holding tanks before the commencement of the processing which utilizes a specific batch of a ~~reagent~~solution. Subsequent to the usage of the batch of solution, the transfer piping system and the ~~blending~~solution prep tank need to be meticulously cleaned in place ~~"CIP" and often SIP procedures~~and sometimes steamed in place prior to the production of the next solution.

Please replace paragraph [007] with the following amended paragraph:

[007] Also, according to the prior art, synchronizing the solution preparation operations to enable the equipment to be utilized well and to ensure the accessibility of all solutions when needed can amount to a substantial challenge and incurs substantial cost. In an ordinary biopharmaceutical and pharamaceutical production facility of the prior art, a significant portion of the space and capital investment is reserved for solution preparation, a distribution system, and a multitude of solution storage tanks. In addition, with batch-wise ~~blending~~solution preparation, the span of scales that can be managed by a specific dimension of tanks and distribution systems is restricted. If the tanks are too limited in volume, they will lack the capacity required for a whole batch or cycle of production. If they are too large, the solutions will remain stationary for too long sometimes allowing inappropriate or economically undesirable chemical changes, and capital investment will be excessive for small scales, leading to a lack of commercial flexibility.

Please replace paragraph [008] with the following amended paragraph:

[008] In more recent years, some biopharmaceutical production facilities have been designed using the concept of producing and storing concentrates of the solutions, which are then diluted ~~online~~in-line with the appropriate pharmaceutical-grade water at the point of use. This approach can reduce the size of the required solution storage tanks, and significantly reduce the number of times batches of solutions must be produced and the storage tanks and distribution systems cleaned. However, the number of storage tanks and the complexity of the distribution systems is not reduced with this approach. Also, the ultimate concentration factor of the storage form of the solution is limited by the solubility of the least soluble component.

Please replace paragraph [0010] with the following amended paragraph:

[0010] Although maintaining batch integrity involves less difficulty to comply with the regulatory requirements of strict traceability of all procedures and materials employed in the production of a given lot of final drug product, there are disadvantages and problems to batch design. The most paramount is the inefficient utilization of equipment capacity. For a significant portion of the time, any given tank or other piece of equipment in ~~the~~a batch-operated plant is simply waiting for the execution of the antecedent steps, for the unit operations, or for the following batch. Meticulous succession and staggering of cycles can aid in the enhancement of capacity utilization; however, the stepwise sequence within the unit operations places a restriction on this approach. There is a viable need to notably enlarge the capacity utilization, particularly for products manufactured on a relatively substantial scale (hundreds of kilograms to tons per year).

Please replace paragraph [0021] with the following amended paragraph:

[0021] According to the current invention, the batchwise, ~~manual blending~~in-vessel generation of pH buffered solutions is improved upon through the use of an ~~automated solution blending~~in-

line solution preparation technique of the current invention. This method utilizes concentrated acids and bases to form the primary buffer solution, and concentrated solutions of salts, surfactants or other additives blended in to form the final solution. In a preferred embodiment of the current invention, a small number of feed solutions is used to make a variety of reagent compositions improving efficiency of operation, decreasing error, and lowering cost. Moreover, the operation may be, in a preferred embodiment, continuous.

Please replace paragraph [0037] with the following amended paragraph:

[0037] The method of the current invention provides an efficient process to produce pH buffered solutions that will ultimately be ~~converted into~~ used in the production of pharmaceutical products or used as pharmaceutical products. The primary ingredients that compose a mixture are water, and a buffer acid and base at a particular concentration and in a particular ratio to produce a desired final pH. In addition, the solution may include other solution ingredients, such as salts, surfactants, inhibitors etc., see detailed listing above. The individual ingredients are blended at the point of use using an automated blending unit

Please replace paragraph [0049] with the following amended paragraph:

[0049] It will be evident from the foregoing description that changes in the form, methods of use, and applications of the elements of the disclosed method for the improved buffer ~~blending~~ preparation and development technology are novel and may be modified and/or resorted to without departing from the spirit of the invention, or the scope of the appended claims.